Anatomical and functional alterations in semantic dementia: a voxel-based MRI and PET study.

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Anatomical and functional alterations in Semantic Dementia: a voxel based MRI and PET study

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Abstract

Rare studies have used MRI and voxel based morphometry (VBM) to assess atrophy, and only two PET studies used SPM to examine functional changes in semantic dementia (SD). Our aim was to highlight both morphological and functional abnormalities in a same group of 10 SD patients, in the entire brain, using a "state of the art" methodology (optimized VBM procedure, PET data corrected for partial volume effects and voxel based analyses). We also used an extensive neuropsychological battery. We showed that main alterations concerned the left temporal lobe, in accordance with the striking impairment of semantic memory in SD patients, as well as the hippocampal region, which may partly explain their moderate episodic memory deficits. Hypometabolism was more extensive than grey matter loss in both temporal lobes, and specifically concerned the orbitofrontal areas, consistent with the moderate impairment of executive functions and behavioural changes. While PET is more sensitive than MRI, there is striking concordance between morphological and functional abnormalities, which contrast with the discordance observed in Alzheimer's disease and might be a typical feature of SD.

1. Introduction

Elisabeth Warrington [76] was the first to describe patients suffering from object recognition and progressive anomia reflecting fundamental loss of semantic memory. There is compelling evidence to consider that this syndrome, termed either temporal variant of frontotemporal dementia [18, 35] or semantic dementia (SD) [70], is part of the disease spectrum of frontotemporal lobar degeneration (FTLD). Although FTLD is a relatively common cause of dementia, accounting for about 20% of cases of dementia with presenile onset, most of cases suffer from the frontal variant of FTD, while the temporal variant is a relatively rare disorder [61]. This disease is characterized by progressive loss of semantic knowledge and relative preservation of grammatical aspects of language, visuospatial skills and day-to-day memory [31, 70], although episodic memory, when specifically assessed, can be impaired [35].

Morphological magnetic resonance imaging (MRI) studies in SD patients show an involvement of the temporal lobe, with an anteroposterior gradient, highest changes concerning the anterior part of the temporal lobe. Left-sided predominant atrophy is more frequent than right predominant or symmetrical involvement (e.g., [7, 26, 29]). Visual inspection of MRI brain scans has suggested that the hippocampal complex is preserved in SD, which might fit with normal day-to-day memory, or near normal performance on episodic memory tests in some patients [27, 28, 57, 58]. Some authors [29, 9] did not find significant atrophy of the hippocampus and adjacent structures using the SPM software which allows a voxel-by-voxel analysis (Voxel Based Morphometry, VBM) of the entire brain. Nevertheless, some studies using the region-of-interest (ROI) method [7, 12, 22, 52] emphasized bilateral hippocampal atrophy, predominant on the left hemisphere. According to Chan et al. [7] and Galton et al. [22] the failure to identify hippocampal abnormality using VBM possibly reflects

the limited resolution of the voxel-by-voxel method for small complex structures such as the hippocampus. Indeed, this technique implies an automated comparison of individual data normalized on a template obtained from normal young control MRI scans, which is not optimal while considering demented patients with atrophied brains. By opposition, Good et al. [25] reported significant hippocampal atrophy in semantic dementia with an optimized VBM technique, i.e. using a customized template obtained from the control and patient samples of the study. Thus, this method is highly recommended while assessing pathologic state associated with brain atrophy, since it helps to reduce the influence of non-brain tissue on the resulting GM statistical probability maps and allows avoiding bias during the spatial normalization step.

Some studies have shown atrophy in other brain regions, notably the frontal lobes [39, 49, 64, 69] and the amygdala [4, 7, 22, 39, 49, 64, 78]. It is worth noting that, with the evolution of the disease, SD patients develop executive dysfunction and behavioural symptoms [18], in accordance with the role of the frontal lobes in behaviour regulation. Concerning the atrophy involving the amygdala, it is well known that this structure has strong links with the processing of emotion as indicated by severe deficits in the recognition of facial expressions in patients with amygdala damage [68]. These emotional impairments may contribute to the behavioural deficits observed in SD.

In sum, only a few studies have applied the VBM procedure in SD [4, 25, 26, 29, 48, 49, 64]. Moreover, two of these studies investigated a small group of patients ([48] N = 4; [49] N = 6), while Rosen et al. [64] compared SD patients with a mixed group of healthy subjects and patients with frontal variant of frontotemporal dementia. Finally, only one study has used the optimized VBM procedure [25] to examine 10 SD patients and the authors showed bilateral atrophy in the inferior, middle and superior temporal lobe, the amygdala, hippocampus and entorhinal cortex with a left hemispheric predominance.

Functional neuroimaging methods such as Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) are more accurate techniques to identify subtle neural dysfunction than morphological MRI [43]. SPECT has been used in few studies to investigate the patterns of regional cerebral blood flow in SD. The results of these studies have principally demonstrated temporal bilateral or left involvement [32, 71] or temporal and frontal bilateral involvement [18]. PET has a better spatial resolution and quantitative accuracy than SPECT, and appears to be a more promising functional imaging technique for the diagnosis and differential diagnosis of dementia [30]. The first PET studies highlighted left temporal lobe involvement [37, 74]. Nevertheless, all these above mentioned studies performed using SPECT or PET used either a visual rating or the ROI method for the analysis of brain images. Both methods are observer-dependent and although the latter is quantitative, it only explores a selected set of structures on the basis of a priori hypotheses, potentially missing other areas. Only two PET studies of regional glucose metabolism used an objective and comprehensive voxel-based analysis, thanks to the SPM software [17, 52] to assess hypometabolism in SD. Diehl et al. [17] reported significant hypometabolism over the whole left temporal neocortex (excluding the hippocampus) and in the right temporal pole. However, actual glucose metabolic values in patients with degenerative diseases measured using PET may be biased because of the partial volume effects (PVE). Indeed, the apparent radiotracer concentration in small structures is influenced by surrounding structures. This phenomenon is particularly dramatic when cortical atrophy is present, such as in degenerative dementia. PVE correction has been applied in the recent study carried out by Nestor et al. [52] who showed hypometabolism in bilateral temporal lobes, including the perirhinal cortex and extending to the fusiform gyrus.

The main aim of our study was to assess both morphological and functional abnormalities in the same group of SD patients, through the entire brain, which has never

been performed yet, using a "state of the art" methodology (i.e. voxel based analyses, the optimized VBM procedure, and PET data corrected for PVE). We also aimed at describing the profile of cognitive impairment in these patients.

2. Material and methods

2.1. Subjects

We studied 10 patients suffering from SD (age: mean = 65.7 ± 8.6 years; range: 54 -79; MMSE mean = 24.2 ± 3.08; disease duration mean = 3.3 ± 2.5) selected according to research criteria of SD established by Neary et al. [50], namely progressive, fluent empty spontaneous speech, loss of word meaning, manifest by impaired naming and comprehension, semantic paraphasias and/or prosopagnosia and/or associative agnosia. For each patient, the selection was made according to a codified procedure in French qualified centres by senior neurologists (VDLS & SB) whose major activity is dedicated to the diagnosis and follow-up of patients suffering from neurodegenerative disorders, as well as a neuropsychologist and a speech therapist. Patients with history of alcoholism, head traumatism, neurological or psychiatric illness were excluded. In all patients, as mentioned by their family, the predominant and inaugural symptom concerned semantic memory deficits reflected by anomia, word comprehension difficulties as well as deficits in the recognition of familiar people. In all our patients the family reported preserved day-to-day memory and autonomy. Indeed, the patients could continue to carry out everyday activities such as do their own shopping, travel around by public transport, keep appointments such as going alone to the physician and remember recent or current events. They were all well oriented in time and space.

We did not exclude patients with episodic or executive disorders, attested by a formal neuropsychological examination, provided that these deficits were not severe, and above all, had not preceded the semantic disorders as attested by family members and/or the clinical staff. Thus, neuropsychological tests carried out on the first examination emphasized semantic

memory deficits and visual episodic memory was totally preserved in most of our patients (8/10) as shown by performances on the recall of the Rey figure [63] and/or the "test de la ruche", a spatial memory task [75]. In the two patients who presented visual episodic deficits at the first examination, one had impaired free recall in contrast with normal recognition performances, and in both patients the deficits were much less severe than those of semantic memory. Finally, the clinical and neuropsychological follow-up of our patients which have been re-examined between 1 to 5 years after their first consultation, has confirmed the initial diagnoses (i.e. the semantic memory deficits were still predominant, and their spatial orientation and autonomy, still preserved).

For the cognitive assessment, patients were compared with 21 control subjects (age: mean = 69.85 ± 8.57 years; range 51-80 years) matched for age and level of education. For the neuroimaging examinations, they were compared to an other independent sample of 17 control subjects from our database (mean: 65.8 ± 7.4 years; range: 57- 84). All were unmedicated, living at home and were strictly screened for lack of cerebrovascular risk factors, dementia or mental disorders. They had neither clinical nor biological abnormalities. The Mattis dementia rating scale [41] was used to exclude any subjects suspected of neurodegenerative pathology.

This protocol was approved by the Regional Ethics Committee. Controls and patients gave written consent to the procedure prior the investigation.

Within a few days interval at most, each subject underwent a neuropsychological examination, a high-resolution T1-weighted volume MRI scan and a resting PET study using [^{18}F] fluoro-2-deoxy-D-glucose (^{18}FDG).

2.2. Neuropsychological exam

We explored semantic memory by means of 1) an oral naming task (DO 80) [13], 2) a semantic knowledge task assessing naming of drawings, categorical and attribute knowledge of concepts [23], 3) a questionnaire assessing knowledge about famous persons [55], 4) a French version of the dead/alive memory test initially worked out by Kapur *et al.* [36], and 5) a categorical (names of animals) verbal fluency tasks [6]. To assess the executive function, following the conception of Miyake *et al.* [45], we investigated the shifting process, inhibition of inappropriate responses and updating function using the trail making test [62], the Stroop test [72] and the running span task [46, 60], respectively. According to Baddeley's model [1] of working memory, we used a dual-task paradigm [2, 60] and backward digit and visuospatial spans to assess the central executive. As regards the slave systems, we assessed the phonological loop and visuospatial sketchpad by using forward digit and visuospatial spans [77]. In order to evaluate visuo-spatial activities, we used the complex figure from the AMIPB (Adult Memory and Information Processing Battery, [11]), and visual episodic memory was assessed with the immediate and delayed recall of the figure. Finally, we used a French version of the "Dysexecutive questionnaire" (DEX) from the Behavioural Assessment of Dysexecutive Syndrome battery (BADS) [80] to assess emotional or personality changes, motivational, behavioural, and cognitive changes (see [42], for details on the cognitive tests).

2.3. Neuroimaging

2.3.1. Data acquisition

The T1-weighted volume MRI scan consisted of a set of 124 adjacent axial cuts parallel to the AC-PC line and with slice thickness 1.5 mm and pixel size 1x1 mm, using the SPGR gradient echo sequence (TR=10.3 s; TE=2.1 kHz; FOV=24*18; matrix=256*192). All the MRI data sets were acquired on the same scanner (1.5 T Signa Advantage echospeed;

General Electric) and with the same parameters. Standard correction for field inhomogeneities was applied at acquisition.

Each subject also underwent a PET scan. Data were collected using the high-resolution PET device ECAT Exact HR+ with isotropic resolution of 4.6 × 4.2 × 4.2 mm (FOV = 158 mm). The patients were fasted for at least 4 hours before scanning. To minimize anxiety, the PET procedure was explained in detail beforehand. The head was positioned on a head-rest according to the cantho-meatal line and gently restrained with straps. ^{18}FDG uptake was measured in the resting condition, with eyes closed, in a quiet and dark environment. A catheter was introduced in a vein of the arm to inject the radiotracer. Following ^{68}Ga transmission scans, three to five mCi of ^{18}FDG were injected as a bolus at time 0, and a 10 min PET data acquisition started at 50 min post-injection period. Sixty-three planes were acquired with septa out (volume acquisition), using a voxel size of 2.2 × 2.2 × 2.43 mm (x y z). During PET data acquisition, head motion was continuously monitored with, and whenever necessary corrected according to, laser beams projected onto ink marks drawn over the forehead skin.

2.3.2. Image handling and transformations

MRI data were analyzed using the optimized VBM protocol, described in details elsewhere [24], and already used in our laboratory [8, 9]. Briefly, the procedure included customized template creation (of the whole brain and of the grey matter (GM), white matter (WM), and cerebro-spinal fluid (CSF) sets) from the MRI data of the whole patient and control samples (n = 27), segmentation and normalization of the original (i.e. in native space) scans using these customized priors to determine optimal normalization parameters, application of these optimal parameters to the original scans, segmentation of the normalized

data and smoothing of the resultant GM partitions, using a 12 mm Gaussian filter. All image processing steps were carried out using SPM2.

The PET data were first corrected for partial volume effect (PVE), taking into account not only the loss of GM activity as a result of spill-out onto extraparenchymal tissues, but also the gain in GM activity as a result of spill-in from adjacent tissues. This method, originally proposed by Müller-Gartner et al. [47] and slightly modified by Rousset et al. [66] is described in details in Quarantelli et al. [59]. All image processing steps were carried out using the 'PVE-lab' software. Using SPM2, corrected PET data were then subjected to coregistration onto their respective MRI and normalization into the same customized template as the one used for normalization of MRI data, reapplying the corresponding optimal normalization parameters. Resultant images were then smoothed using a classical Gaussian kernel of 14 mm, to blur individual variations and to increase the signal-to-noise ratio. In order to remove the confounding effect of intersubject variability in global CMRglc, the CMRGlc images were divided pixel by pixel by the individual value for the cerebellar vermis (this value being not statistically different from controls), as classically performed in previous studies [14, 15, 16, 19].

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2.4. Data analyses

For each cognitive test measure, we performed Mann-Whitney analyses to assess between-group comparisons. Statistics were considered as significant using a $p<0.05$ threshold.

Regarding MRI and PET data, we assessed group differences to obtain maps of significant atrophy and significant hypometabolism in patients with SD compared to controls, using the "compare-populations: 1 scan/subject" SPM2 routine. In order to minimize "edge effects",

only those voxels with values above 10% of the mean for the whole brain were selected for statistical analyses. For both analyses of GM loss and hypometabolism, we used a stringent threshold of $p<0.05$ FWE (family wise error, the standard measure of type I errors in multiple testing, see [53]) corrected for multiple comparisons, with a minimum cluster size of 100 voxels, to limit the risk of false positives. For the sake of completeness, the reverse contrasts were also assessed (i.e. greater GM loss or hypometabolism in Controls).

3. Results

3.1. Neuropsychological data

Results of the Mann-Whitney analyses for each test are listed in Table 1. Impairment of semantic memory was severe, as attested by significantly lower performances in SD compared to controls in all semantic memory tasks of the extensive neuropsychological examination. This examination also revealed an impairment of the shifting process (Trail Making test) and the inhibition of inappropriate responses (Stroop test) in contrast with the preservation of the updating function (running span task). The working memory was preserved, as shown by the dual-task paradigm and backward digit and visuo-spatial spans, as well as forward digit and visuospatial spans. Visuospatial abilities were also preserved as pointed by the copy of the Amipb figure. The patients showed a clear-cut impairment of episodic memory, as assessed by the immediate and delayed recall of the Amipb figure. Finally, the 6 patients who underwent the "Dysexecutive Questionnaire" (DEX) presented various behavioural changes. Indeed, they were apathetic and exhibited reduced empathy and stereotypic behaviours. Among the 4 patients who did not undergo the DEX questionnaire, two presented behavioural disturbances (agitation and obsessional disorders), as attested by their family.

3.2. Neuroimaging data

Figure 1 (top) illustrates the significant GM loss in SD patients compared with controls, and the most significant peaks are listed in Table 2. Regions of significant loss, largely predominant in the left hemisphere, involved the whole left temporal neocortex (temporal pole and inferior, middle and superior temporal gyri), extending to the hippocampal region (hippocampus, parahippocampal gyrus, amygdala), as well as the left insula, thalamus, caudate nucleus and fusiform gyrus. The left anterior cingulate cortex was also involved although less significantly. On the right side, the GM loss was less significant and only concerned a small part of the temporal neocortex as well as the hippocampal region (also including the hippocampus proper, parahippocampal gyrus and amygdala), extending into the fusiform gyrus. There was no significant cluster when assessing the reverse contrast.

Figure 1 (bottom) illustrates the significant hypometabolic regions in SD patients compared with controls, and Table 3 lists the most significant peaks. Regions of significant hypometabolism were roughly the same as those of significant GM loss, although the overall pattern of brain hypometabolism was more extended. They were bilateral but more extensive on the left side, and involved the temporal lobe, including both the temporal neocortex (temporal pole, and inferior, middle and superior gyri) and the hippocampal region (including the hippocampus proper, parahippocampal gyrus, and amygdala), and also encroaching the fusiform gyrus. Bilateral hypometabolism also concerned insula, caudate nucleus, anterior cingulate and orbitofrontal areas. The reverse contrast did not reveal any significant cluster.

Thus, hypometabolism was more extensive than GM loss in both temporal lobes, but more in the right one and it also involved the bilateral orbitofrontal areas (BA 11), right caudate nucleus and insula, while these areas did not show significant atrophy at the same threshold. Conversely, there was no area of significant atrophy without significant hypometabolism.

Finally, in an exploratory way, we then searched for positive correlations between morphometric and metabolic data on the one hand, and cognitive performances on the other hand. Given the small number of patients, we limited this research to one issue, that of the involvement of left versus right temporal lobe in the alteration of semantic memory. We correlated semantic memory performances with the mean morphological or metabolic values obtained for each temporal region, using a non-parametric correlational analysis (Spearman test). These values were extracted using the "functional ROI analysis" of the fMRI-ROI SPM toolbox (which allows to obtain the mean value of each ROI of interest included in each cluster). Regarding morphological data, we found significant ($p<0.05$) correlations, all being left-sided situated, between 1) naming performances and the temporal pole and superior temporal gyrus ($r = 0.64$ and 0.73, respectively), 2) categorical fluency and the inferior temporal gyrus ($r = 0.61$) and 3) semantic knowledge performances and the superior temporal gyrus ($r = 0.57$). Regarding metabolic data, scores obtained at the Dead or Alive test were significantly correlated with the temporal pole ($r = 0.57$), fusiform gyrus ($r = 0.66$) and parahippocampus ($r = 0.60$), all in the right hemisphere.

4. Discussion

In this study we have used an extensive neuropsychological assessment to further describe the profile of cognitive impairment in a group of 10 SD patients. Our main aim was to examine both morphological and functional cerebral changes in the same group of patients, thanks to a rigorous and up to date methodology, including 1) an optimized VBM procedure, 2) the correction of PET data for PVE, 3) the use of identical normalization parameters for both neuroimaging modalities data sets (thus avoiding bias due to differences in these handling steps between MRI and PET data), and finally 4) the same stringent threshold for

assessing both atrophy and hypometabolism statistics, providing thus a high degree of confidence in our findings.

Semantic memory was severely impaired in our group of patients, whatever the type of stimulus assessed (concepts or famous persons), and whatever the task used (naming, knowledge assessment or categorical fluency), in accordance with the literature [31, 33, 56]. Regarding executive functions, this group of SD patients showed a deficit of inhibition and shifting processes, in contrast with the preservation of updating. Working memory was preserved whatever the component assessed, either the central executive, or the slave systems, a pattern of results similar to that shown by Hodges and colleagues [34, 56]. Visuospatial abilities were also preserved [56, 38], while visual episodic memory was impaired. Even if SD is characterized by preserved day-to-day memory [50], our finding is in keeping with previous reports showing deficient performances on standard episodic memory tests [35]. While episodic memory deficits could be partly due to semantic memory impairments, the use of a visual episodic task in our study suggests genuine episodic memory impairment, although definitely less serious than in Alzheimer Disease patients [52, 58]. Finally, all the patients who underwent the behavioural assessment presented various changes, in line with growing evidence that many patients with SD have behavioural changes, sometimes identical to those suffering from the frontal variant of frontotemporal dementia [5, 18, 39, 54, 65, 67].

The findings of our MRI study highlight, as expected, significant GM reduction in the left temporal neocortex (temporal pole, and inferior, middle and superior temporal gyri), and at a lesser degree, in the right temporal neocortex, in accordance with previous quantitative volumetric [7, 22, 39] and VBM [4, 25, 26, 29, 49] studies. This pattern of results is in agreement with the severe semantic memory deficits in our group of SD patients.

The GM reduction was also found to concern at a lesser degree the left fusiform gyrus, consistently with previous studies in SD [22, 26, 49], as well as in the amygdala, parahippocampal gyrus and hippocampus, predominantly on the left hemisphere. Left amygdala atrophy in SD has recently been shown in VBM [4, 25] and in volumetric [39, 78] MRI studies, and seems to be more pronounced than in Alzheimer's disease. Davies et al. [12] have also stressed the involvement of the parahippocampal gyrus, more precisely, the perirhinal and entorhinal cortices, in SD. Our findings regarding the hippocampus are in keeping with the study of Good et al. [25] which used an optimized VBM procedure. The presence of significant atrophy in this region has also been reported in other studies using the ROI method [7, 22, 52]. In contrast with our findings, these latter authors showed that medial temporal lobe damage in SD was not associated with episodic memory deficits. However, their study was designed to contrast the patterns of brain alterations between SD patients with selective semantic memory deficits and Alzheimer's disease patients with episodic memory deficits, instead of providing the brain profile of alteration representative of SD pathology. Their SD patients have thus been specifically selected for this purpose as being free from episodic memory deficits.

We also reported significant atrophy in the left insula, anterior cingulate cortex, thalamus and caudate nucleus in our group of patients, in accordance with Gorno-Tempini et al.'s VBM study [26].

Regarding PET data, we showed a bilateral temporal lobe hypometabolism, consistent with the two previous voxel based PET studies [17, 52]. It is worth noting that both studies did not report additional areas of significant hypometabolism. By contrast, we found a metabolic defect in the bilateral hippocampal region as well as in the bilateral orbitofrontal areas, right caudate nucleus and insula. While the former structures also showed an extended

atrophy, the latter regions were not significantly atrophied at the same threshold. Although the hypometabolism of orbitofrontal areas had not been described yet, morphological alterations of this region have been reported [18, 49]. This result fits on the one hand with the deficit of inhibition processes, in contrast with the preservation of other executive processes, such as updating, mainly subtended by the frontopolar cortex [10], and on the other hand, with behavioural changes of the patients. It is worth noting that a recent VBM study [65] supports the involvement of the right orbitofrontal cortex in disinhibition in FTD/SD patients. However, Williams et al [79] found that this area appeared to correlate with semantic performances but not with behavioural changes. Thus, orbitofrontal damage appears as a common feature of SD cases but what it means to the clinical expression remains an open question.

Altogether, our findings revealed a broader than previously described pattern of hypometabolism in SD. This finding might be due to the fact that we studied a group of patients suffering from an advanced disease stage and/or to the use of a rigorous methodology. The first hypothesis would fit with their impairment of some executive functions and visual episodic memory, but seems insufficient to explain such findings since semantic dementia patients free from all other deficits than semantic memory are likely to be rare. Moreover, in the two previous PET studies [17, 52], the dementia severity, as assessed with the MMSE [21] was similar to that of our patients. Regarding the study of Nestor et al., the differences are probably due to the criteria selection (see above). Although methodological improvements might account for the specific findings of the present study compared to Diehl et al. (see methodological section), one other plausible explanation for differences in this study compared to the other two SPM studies is that any two cohorts of degenerative brain disease are likely to have some idiosyncrasies that reflect the individual cases. Overall, except for orbitofrontal metabolic abnormalities, there is a good concordance

between our findings and those of Diehl et al. [17] who reported significant hypometabolism over the whole left temporal neocortex and in the right temporal pole and Nestor et al. [52] who showed hypometabolism in bilateral temporal lobes, including the perirhinal cortex and extending to the fusiform gyrus.

Regarding the differential contribution of the right and left temporal lobes to semantic knowledge impairment in SD, findings from our exploratory correlational analysis suggest a predominant role of the dysfunction of the left temporal lobe in word-finding difficulties and in general semantic knowledge, while the right counterpart would be implicated in the impairment of person-specific knowledge. Consistent with this interpretation, several studies have reported significant correlations between semantic memory deficits and GM loss in the left temporal neocortex in SD [29, 49]. More recently, Williams et al. [79] have revealed in a group of frontotemporal dementia patients (including both temporal and frontal variants) that semantic breakdown, measured by non-verbal associative knowledge and naming, was mainly correlated with extensive loss of GM volume throughout the left anterior temporal lobe. Our findings also fit with those of Thompson et al. [73] who showed different patterns of cognitive disturbances (predominant in the domain of word-finding and person-specific knowledge, respectively) according to the predominantly altered temporal lobe. Other authors have suggested the right temporal lobe to be critical to person-specific knowledge (e.g., [20]).

To conclude, hypometabolism is more extensive than atrophy in the temporal lobes and specifically concerns the bilateral orbitofrontal areas, right caudate nucleus and insula. However, most of the regions of significant hypometabolism were about the same as those areas of significant GM loss and were also mainly left-lateralized. The relative overlap between morphological and functional abnormalities in SD contrasts with the discordance observed in Alzheimer’s disease [3] and patients at a pre-dementia stage of Alzheimer's [8].

Indeed, in this pathology, while the temporal lobe is the first to be atrophied, the posterior cingulate-precuneus area is the highest and earliest functionally altered region. This discrepancy between both profiles suggests that functional changes may be caused partly by remote effects from the morphologically altered hippocampus, while this region would be the site of a compensatory response by neuronal plasticity [8, 40, 44, 51]. The current findings also accord with those of Nestor et al [52] who found that metabolism and atrophy in mesial temporal ROIs were correlated in SD but not in AD. Thus, the consistency between morphological and functional abnormalities in SD might be a typical feature of this disease and would be useful to better differentiate SD from AD.

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Disclosure Statement

All authors, Béatrice Desgranges, Vanessa Matuszewski, Pascale Piolino, Gaël Chételat, Florence Mézenge, Brigitte Landeau, Vincent de la Sayette, Serge Belliard, and Francis Eustache, certify that the data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

None of the authors have actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) their work. No author's institution has contracts relating to this research through which it or any other organisation may stand to gain financially now or in the future.

All authors have reviewed and agreed upon the final paper submitted for publication and validate the accuracy of the data.

This study was done in-line with the declaration of Helsinki following approval by the Regional Ethics Committee

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Table 1. Neuropsychological data (m ± σ) for 10 SD and 21 control subjects.

Cognitive functions		Tests	Controls	Patients	Group effect (U Mann-Whitney test)
Semantic memory		Picture naming test (DO 80)	79.57 (1.1)	45.9 (22.03)	***
		Semantic Knowledge test (/236)	232.38 (3.6)	185.78 (38)	***
		Famous People test (/40)	39.84 (0.6)	25.50 (16)	***
		Dead or Alive test (/13)	10.01 (2.5)	4.34 (3.1)	**
		Categorical fluency	26.47 (7.5)	10.22 (5.3)	**
Executive Function		Trail Making Test B (seconds)	133.47 (65.5)	225.88 (99.7)	*
		Stroop (Word Color)	48.28 (6.9)	33.3 (9.1)	**
		Running Span task (/16)	7.33 (4.1)	4.67 (2.1)	NS
Working memory	Central executive	Dual task (level of performance, in %)	71.98 (18.4)	67.29 (8.5)	NS
		Backward digit span	4.14 (0.9)	4.25 (1.3)	NS
		Backward visuo-spatial span	4.24 (0.8)	3.75 (1.03)	NS
	Slave systems	Forward digit span	5.76 (0.9)	5.75 (1.03)	NS
		Forward visuo-spatial span	4.71 (0.6)	4.75 (1.2)	NS
Visuospatial abilities		Copy of the Amipb figure (/76)	75.04 (1.5)	75.44 (1.3)	NS
Episodic memory		Amipb figure, Immediate recall (/76)	45.29 (16.6)	22.44 (19.4)	**
		Amipb figure, Delayed recall (/76)	45.95 (15.4)	24.33 (20.4)	**

Significant differences between patients and controls: *: $p<0.05$; **: $p < 0.01$; ***: $p<0.001$; NS : non significant

Table 2. MRI data: significant (p <0.05 FWE corrected and k> 100) atrophy in SD compared to controls.

MNI			T	k	Label	BA	% label
-57	-12	-23	10.62	32322	L Temporal Pole	20, 21, 38	16.9
					L Inf Temporal G	20	14
					L Mid Temporal G	20, 21, 22	19.1
					L Sup Temporal G	21, 22	31.2
					L Parahippocampus	28, 35, 36	32.4
					L Hippocampus		70.6
					L Amygdala		74.9
					L Fusiform G	20	15.2
					L Thalamus		3.3
-31	20	2	8.18	4430	L Insula		18.9
					L putamen		4.2
23	-14	-14	8.06	4525	R Parahippocampus	28, 35, 36	11.2
					R Hippocampus		30.2
					R Amygdala		16
40	-10	-10	8.04	1204	R Inf Temporal G		2.3
					R Fusiform G	20	1.8
-8	26	1	7.37	3145	L Caudate		11.4
					L Ant Cingulate G	24	6.4
35	14	-41	7.31	181	R Mid Temporal	20	1.8

Location and MNI coordinates of peaks of significant GM reduction in SD patients compared to Controls (in decreasing order of significance). Cluster size is indicated by k= number of voxels in the particular cluster. Labels and percentage of the labelized region belonging to the cluster were obtained for each significant cluster using the automated anatomical labeling (AAL) Toolbox.

MNI = Montreal Neurological Institute; BA = Brodman area; L = left; R= right; G = gyrus; inf = inferior; ant = anterior; mid = middle; sup = superior.

Table 3. PET data: significant (p<0.05 FWE corrected) hypometabolism in SD compared to controls.

MNI coordinates			T	k	Label	BA	% label
-28	5	-35	8.43	62184	L Temporal Pole	20, 21, 38	79.1
					L Inf Temporal G	20	49.5
					L Mid Temporal G	20, 21	14.1
					L Sup Temporal G	21	9.1
					L ParaHippocampus	28, 35, 36	51.8
					L Hippocampus		60.6
					L Amygdala		61.9
					L Fusiform G	20, 36	32.8
					L Insula		27.1
					L Orbitofrontal G	11	8.4
-13	4	24	7.01	53349	R Temporal Pole	20, 21, 38	40.4
					R Inf Temporal G	20	11.3
					R Mid Temporal G	20, 21	3.4
					R Sup Temporal G	21	1.7
					R ParaHippocampus	28, 35	32.5
					R Hippocampus		11.2
					R Fusiform G	20, 36	15
					R Insula		1.5
					L & R Caudate		62 & 21.3
					L & R Ant Cingulate G	24/32	13.2 & 5.2
					L & R Rectus G	11	13.9 & 10.8
					L & R Orbitofrontal G	11	12.1 & 8.9

Location and MNI coordinates of peaks of significant hypometabolim in SD patients compared to Controls. Cluster size is indicated by k= number of voxels in the particular cluster. Labels and percentage of the labelized region belonging to the cluster were obtained for each significant cluster using the automated anatomical labeling (AAL) Toolbox.

MNI = Montreal Neurological Institute; BA = Brodman area; L= left; R = right; G = gyrus; inf = inferior; ant = anterior; mid = middle; sup = superior.

Legend Fig 1

Clusters of significant ($p<0.05$ FWE corrected; $k > 100$ voxels) atrophy (top), and hypometabolism (bottom), in patients with SD compared to controls, as superimposed onto axial slices of the customized template.